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Anisotropic Internucleosome Interactions and Geometrical Constraints Favour the Two-Start Helical Structure of Chromatin

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The structures of chromatin at the high density characteristic of the silent phase are strongly influenced by the packing of nucleosome core particles (NCPs), the anisotropic attractive interactions between two of them and constraints, such as the DNA bending, imposed to the wrapped and linker DNA segments. In this work, coarse–grained models of chromatin are studied. For a pair of NCPs, a simple single–site anisotropic potential energy function is designed on the basis of the experimental data reported for the ordered phases of NCPs. This potential energy function is employed in random–walks of chromatin models where the NCP DNA wrapping is modulated in length, while the linker segments are modulated in both length and curvature. These models support the two–start helical organization for chromatin in the absence of linker histones. The geometry of two-start helical configurations is characterized by poorly bent linkers and by a moderate reduction of wrapped DNA in the NCP.

1 Introduction

The investigation of the supramolecular structure and dynamics of chromatin is of extreme importance to understand gene regulation and cell development. The genetic information in eukaryotic chromosomes is organized in chromatin, a chain–like supramolecular assembly formed by a long filament of DNA wrapped around globular octameric aggregates of eight histone proteins[1]. The repeat unit of this chain includes a nucleosome core particle (*i.e.* the complex of a protein histone octamer with DNA wrapped around it, NCP hereafter) and a DNA linker, which connects two NCPs. Other histone proteins in the linker region are present in the natural chromatin and absent in several model systems studied in vitro.

Two classes of organizations have been proposed for the compact state of chromatin, *i.e.* the so–called 30 nm fiber[2,3]: the one–start solenoidal helix model[4]; the two–start helix model[5]. Recent crystallographic results for the tetra–nucleosome molecule in the absence of linker histones[6], provide strong evidence for the two–start helix organization: the structure of the tetra–nucleosome is consistent with an idealized model where two left–handed twisted ribbons follows a straight fiber axis. These x-ray data are also consistent with the high propensity of NCPs of forming columns[7]. Theoretical and computational

models of the chromatin fiber have been proposed, but two–start helices with the geometry of the x-ray data were never identified among the proposed structures.

In this work, a single–site anisotropic Lennard–Jones interaction potential, calibrated on the experimental phase transition for NCPs, is used to perform random walks of chromatin models with a variable amounts of wrapped and linker DNA segments and with linker DNA with variable curvature.

2 Method

The geometrical construction of regular chains of many NCPs is summarized in the following. The pathway of DNA is built starting by wrapping n_w bp around the disc representing the histone octamer (radius of 4.5 nm and height of 6 nm). When the DNA finishes to wrap, a straight linker of n_{s1} bp follows. At a certain point, DNA starts to bend (n_b bp) around an origin **O** chosen at random within a cubic portion of space. Two curvatures have been tested, with no significant differences in results. The DNA has no kinks. A second straight linker segment of n_{s2} bp follows. Before the next NCP particle is generated, a further rotation of $\Delta\Phi$ modifies the orientation, otherwise imposed by the equilibrium twisting of DNA.

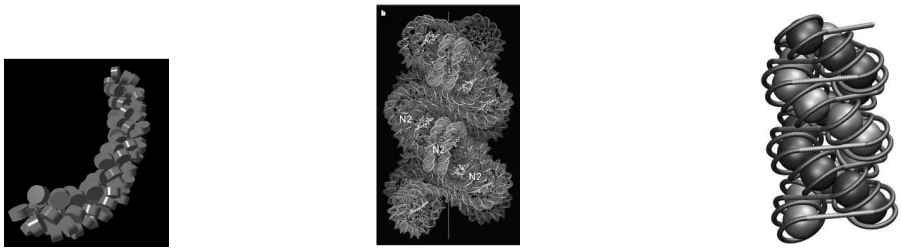
Monte Carlo trajectories have been collected using a temperature randomly chosen within 0 and 10000 K and using the NCP–NCP interactions only. Among the collected configurations, the linker–linker interactions have been computed by using a Lennard–Jones site for each DNA bp, with a σ parameter of 1 nm. Only those configurations with negative linker–linker potential energy and with low NCP–NCP interaction and high compactness have been selected and analyzed.

3 Results

The distribution of the supplemental bending angle (Θ) and of the torsional angle (Φ) of the selected chains has been analyzed. This distribution always displays a maximum around $\Theta \sim 5\pi/6$ and $\Phi \sim \pi/2$. Structures representative of this region display the two–start organization, with linker DNA almost perpendicular to the fiber axis. One of these structures is compared with the experimental x-ray data and with a previous simulation in Fig. 1.

The structures obtained by previous MC simulations using similar parameters (panel a) could display only a partial two–start organization, because of the low regularity. The representative structure obtained in this work (c) is very close to the construction based on x-ray data (b). The NCP planes are only slightly tilted away from the fiber axis compared to the tetra–nucleosome. The linker DNA segments are straight, but a local bending can be suggested by linker–NCP interactions that have been ignored so far. The wrapped length of the most representative configurations is about 130 bp, that is in close agreement with the value of 129 bp found in the tetra–nucleosome.

Therefore, this simple chromatin model accounts for most of the important features of the available structural information for chromatin in the absence of linker histones. The role of the interactions included in this model can be summarized: NCP–NCP interactions



(a) (b) (c)

Figure 1. Comparison between the most representative structure in this model (c), MC simulations (a) and the x-ray data (b): one snapshot of the simulation in Ref.[8] (a); the construction obtained from the tetra–nucleosome x-ray data[6] (b); one of the structures representative of the maximum population in the two–angles map (this work, c). In (c) the large spheres represent the histone octamers (dark gray the even numbers, light gray the odd numbers to emphasize the two–start organization). The small spheres represent DNA bp. The radii of these latter spheres is 1/2 of the used value for graphical purposes.

favour columns (like those experimentally observed); wrapped and linker DNA favour the coiling of columns; these columns can not be coiled enough to obtain a dense one–start organization (solenoid); on the other hand, two less coiled columns intercalated allow the two–start organization; crossed linkers allow a moderate DNA–NCP overlap; the unfolding of the two–start organization is not intricate.

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